REMARKS

The Official Action of 6 September 2007 has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claim 12 has been amended by limiting the claimed method to the treatment of subjects, including animals and humans, that have had a decrease in functional liver cell loss in accordance with the disclosure in the specification as filed at, for example, page 2, lines 3-11 and 19-23, and page 6, lines 5 to 31. Claim 14 has been amended by limiting the claimed method to preventing liver damage in subjects prior to a transplant or hepatectomy in accordance with the disclosure in the specification as filed at, for example, the paragraph bridging pages 1 and 2, the first full paragraph on page 2 and the Examples (see, e.g., Example 8 on pages 13-16). The dependent claims have been amended to reflect the changes made in claims 12 and 14, and new claims 28-33 have been added more completely to define the subject matter which Applicants regard as their invention. The recitations in claims 31-33 are supported in the specification as filed at, for example, page 1, lines 11-12 and page 16, lines 29-30.

Applicants respectfully submit that the amendments to claims 12 and 14 remove the basis for the rejection under 35 USC 102(b) for alleged anticipation by Jin et al appearing at pages 8-9 of the Official Action. The rejection is based upon alleged inherency insofar as the Examiner considers Jin et al to teach a process of administering CT-1 protein to mice

and appears to contend that such administration would inherently have stimulated hepatic regeneration in the mice and would inherently have had an effect in preventing liver damage.

Even assuming for the sake of argument that this were true, the cited art cannot be said to anticipate, either expressly or inherently, the method defined by the claims as amended of treating with the administration of CT-1 a subject **whose liver has experienced a loss of functional liver cells or** a subject **prior to the subject undergoing a liver transplant or hepatectomy**. Indeed, this follows from the acknowledgment made by the Examiner in the Official Action of 11 December 2006 at page 11: "While the prior art teaches the administration of cardiotrophin-1 to stimulate liver growth, see Jin et al above, the prior art of record does not teach or suggest administering cardiotrophin-1 to stimulate hepatic regeneration in patients with chronic liver diseases, cirrhosis, or hepatitis, or in patients following hepatectomy or liver transplant.". The cited art not only does not teach or suggest administering CT-1 to patients with these diseases or conditions, it does not teach or suggest administering the same to patients who are about to undergo liver surgery or who have suffered a loss of functional liver cells **in any circumstance**. Accordingly, the amendment to the claims respectfully removes the basis for the prior art rejection.

The claims as amended are also free of the rejection under 35 USC 112, first paragraph for alleged lack of enablement. The reasons advanced by the Examiner for the rejection are as follows:

(1) the working examples teach the intravenous administration of Ad-CT-1, not CT-1 polypeptide, and do not show the stimulation of hepatic regeneration;

(2) the specification allegedly provides no guidance concerning the dosage, route of administration or the number of protein administrations required to achieve a therapeutic effect on hepatic regeneration;

(3) the prior art teaches that intraperitoneal administration of CT-1 protein results in numerous side effects;

(4) the prior art teaches that alcoholic hepatitis and cirrhosis are life-threatening diseases for which few treatments are currently available; and

(5) the specification is silent as to the treatment of intrahepatic tumors using CT-1.

Applicants respectfully submit that a consideration of the relevant factors (the "Wands factors", see MPEP 2164.01(a)) shows that the specification enables the practice of the invention as now claimed without undue experimentation. Such consideration is provided next in connection with the Declaration under 37 CFR 1.132 submitted herewith.

Applicant first respectfully notes that it would be improper to base an enablement rejection on any one of the Wands factors alone, such as the presence or absence of working examples as in (1), above. See MPEP 2164.01(a) ("It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the

evidence as a whole."). Moreover, with regard to the accuracy of an applicant's asserted utility, this may be established by reasonable correlation. See MPEP 2107.03(I) ("The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use.").

The Declaration of Dr. Jesus Prieto Valtuena submitted herewith shows that one of skill in the art could have routinely practiced the method as presently claimed without undue experimentation based upon the guidance in the specification and the knowledge available to those of skill in the art as of the application filing date. Specifically, the declaration shows that, as of the application filing date, one of skill in the art could have routinely selected a dosage/regimen for CT-1 administration based on the state of the art (one of the Wands factors) that would have been expected to result in the stimulation of hepatic regeneration based on the teachings in the specification as filed. Moreover, the Declaration shows that Applicants were in fact able to reproduce the hepatoregenerative effects obtained with Ad-CT-1 by administration of recombinant CT-1 using techniques available as of the application filing date, as next discussed.

Exhibit 2 of the Declaration consists of two articles published after the priority date of the present application, wherein "in vivo" experimental support of CT-1 recombinant

protein administration is shown. In both articles, Dr. Prieto is one of the authors. In the article of Iñiguez et al, the experimental animal model used (see first paragraph of the section "Material and methods") followed the experimental protocol of reference (23), which dates from 1999. In the article of Marquès et al, the animal studies were carried out from commercial sources and following the protocol given in reference (10) that dates from 2001. Accordingly, as of the application filing date, the experimentation techniques used for the "in vivo" (mice model) assessment of the hepatoregenerative and hepatorprotective effects attributed to CT-1 recombinant protein were part of state of the art.

While the Declaration submitted herewith shows that one of skill in the art could have routinely effected the administration of CT-1 to an animal **without adverse side effects** based on the specification as filed using knowledge available to those of skill in the art as of the application filing date, the enablement determination should be made on statutory requirements for patentability, not on safety considerations. See MPEP 2107.03 ("Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness."). Furthermore, the claims as amended do not require the treatment of life-threatening diseases, such as alcoholic hepatitis or cirrhosis, or the treatment of intrahepatic tumors, but only require the administration of CT-1 in an amount effective for protecting the liver of a subject about to undergo liver surgery or for stimulating hepatic regeneration in a subject who has experienced loss of functional liver cells (irrespective of whether this results in treatment of a specific disease).

Accordingly, the breadth of the amended claims (one of the Wands factors) is respectfully believed to be such as to remove the bases for rejection under (4) and (5), above for at least this reason. (Applicants also note that, as provided in MPEP 2107.03, a utility rejection is only appropriate where an asserted utility is not credible--not the case here.).

Applicants respectfully submit that, when considered as a whole, the evidence in the present case, and in particular in the Declaration submitted herewith, leads to the conclusion that the specification is enabling for the invention as now claimed. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 USC 112, first paragraph.

In view of the above, Applicants respectfully submit that all rejections and objections of record have been overcome and that the application is now in allowable form. An early notice of allowance is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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